REMARKS

The Final Office Action of November 20, 2003, has been received and reviewed. Claims 2, 21, 25, 28-32, 37, 44, 50, 51, 54, 56-62, 64, 65 and 69-71 are currently pending. Claims 28-32 stand allowed and claims 2, 21, 25, 37, 44, 50, 51, 54, 56-62, 64, 65 and 69-71 stand rejected. Applicants propose to amend claims 2, 25, 37, 44, 58, 60, 65, 69 and 71 and cancel claims 50, 64 and 70 as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 2, 21, 25, 37, 44, 50, 51, 54, 56-62, 64,65 and 69-71 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter that is not reasonably enabled by the specification. At least partially in view of the proposed amendments to claims 2, 25, 37, 44, 58, 60, 65, 69 and 71, applicants respectfully traverse the rejections as set forth herein.

It was thought that the specification fails to disclose the structural features of various adenovirus fiber proteins that contribute to the reduced tropism for liver cells or increased tropism for endothelial cells and smooth muscle cells. However, the specification indicates that the "C-terminus, or knob [of the fiber protein], is responsible for initial interaction with the cellular adenovirus receptor." (Specification, as-filed, page 5, lines 7-9). Thus, the knob of the fiber protein is a structural feature that, when changed as disclosed in the as-filed specification, contributes to the reduced tropism for liver cells or increased tropism for smooth muscle cells and endothelial cells. (*See*, *Id.* at Example 2, pages 37-38 and under heading "B) Infection of human smooth muscle cells," pages 40-41).

The Final Office Action further indicated that the specification "does not reasonably provide enablement for recombinant adenovirus 12, 16, 28, or 40-L comprising any tissue determining fragment with a reduced tropism for liver cells, an adenovirus capsid with a reduced tropism for liver cells comprising proteins from at least two different adenoviruses and at least one protein [that] includes a tissue tropism determining fragment of a fiber protein of adenovirus 12, 16, 28, or 40-L." (Final Office Action, page 2). Although applicants do not agree that any of

the claims lack compliance with the enablement requirement, to expedite prosecution, applicants propose to amend independent claims 2, 25, 37, and 69 as set forth herein.

As proposed to be amended, independent claim 2 is directed to a recombinant adenovirus of a subgroup C origin having a reduced tissue tropism for liver cells. The recombinant adenovirus of amended claim 2 comprises a capsid having a chimeric fiber protein, wherein a knob domain of the chimeric fiber protein is of an adenovirus origin selected from the group consisting of adenovirus 12, adenovirus 16, adenovirus 28 and adenovirus 40-L.

With regard to claim 25, applicants propose to amend it to read on an adenovirus capsid having a reduced tissue tropism for liver cells. The adenovirus capsid of amended claim 25 comprises a fiber protein of an adenovirus of subgroup C origin, wherein a knob domain of the fiber protein is of an adenovirus origin selected from the group consisting of adenovirus 12, adenovirus 16, adenovirus 28, and adenovirus 40-L.

As proposed to be amended, claim 37 is directed to a method for reducing a tissue tropism of an adenovirus capsid of a subgroup C origin for liver cells. The method comprises exchanging a first nucleic acid encoding a knob domain of a fiber protein of the adenovirus of subgroup C origin for a second nucleic acid encoding a knob domain of a fiber protein of an adenovirus selected from the group consisting of adenovirus 12, adenovirus 16, adenovirus 28, and adenovirus 40-L.

As proposed to be amended, claim 69 is directed to a recombinant adenovirus capsid having a reduced tissue tropism for liver cells comprising a chimeric fiber protein comprising at least the knob domain of a fiber protein of adenovirus serotype 16, wherein the remaining part of the fiber protein is of an adenovirus of a subgroup C origin.

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied." (M.P.E.P. § 2164.01(b), *citing In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)).

The as-filed specification provides working examples of recombinant adenoviruses that correlate to the scope of the recombinant adenovirus of claim 2, the adenovirus capsid of claim 25, the method of producing a recombinant adenovirus of claim 37, and the recombinant

adenovirus capsid of claim 69. For instance, the as-filed specification indicates that nucleic acids encoding the knob region of the fiber protein of adenoviruses 12, 16, 28 and 40-L were amplified. (*See*, Specification as-filed at page 33, lines 5-25 and Tables I and III). The amplified nucleic acids encoding the knob region of fiber proteins of adenoviruses 12, 16, 28 and 40-L were inserted into a vector lacking the knob region of the fiber protein of adenovirus 5, *i.e.*, of a subgroup C origin. (*See*, *Id.* at page 33, lines 28 through page 35, line 4). The vectors were used to produce a recombinant adenovirus (*See*, *Id.* at page 34, line 6 through page 35, line 27), and the resulting recombinant adenoviruses were injected into rats in order to ascertain the biodistribution of the recombinant adenoviruses. (*See*, *Id.* at page 37, Example II). Table II on page 47 of the as-filed specification indicates that recombinant adenoviruses of a subgroub C origin and having a knob region of the fiber protein originating from adenoviruses 12, 16, 28, and 40-L had a reduced tissue tropism for the liver. (*See*, *Id.* at page 47, Table II).

Thus, one of ordinary skill in the art would be able to make and use the recombinant adenovirus and capsid having a reduced tissue tropism for liver cells of claims 2, 25, and 69 respectively, and perform the method for reducing a tissue tropism of an adenovirus capsid for liver cells of claim 37 without undue experimentation.

The Final Office Action further indicated that the specification does not reasonably provide enablement for "a recombinant adenovirus comprising a recombinant adenovirus capsid having peptides from at least two different adenoviruses and at least one of said peptides comprises a tissue determining fragment of a fiber protein of adenovirus 11, 16, 35, or 51." (Final Office Action at page 3). Although applicants do not agree that any the claims lack compliance with the enablement requirement, to expedite prosecution, applicants propose to amend independent claims 44, 50 and 60 as set forth herein.

As proposed to be amended, claim 44 is directed to a recombinant adenovirus of a subgroup C origin having an increased tropism for smooth muscle cells. The recombinant adenovirus comprises a recombinant adenovirus capsid comprising a fiber protein, wherein at least a knob domain of the fiber protein is of an adenovirus of subgroup B origin. The

adenovirus of subgroup B origin is selected from the group consisting of adenovirus 11, adenovirus 16, adenovirus 35, and adenovirus 51.

Regarding claim 58, applicants propose to amend it to read on a recombinant adenovirus capsid having an increased tissue tropism for smooth muscle cells. The recombinant adenovirus capsid comprises a chimeric fiber protein, wherein a knob domain of the chimeric fiber protein is of an adenovirus of subgroup B origin, and wherein the adenovirus of subgroup B origin is selected from the group consisting of adenovirus 11, adenovirus 16, adenovirus 35, and adenovirus 51. A remaining part of the chimeric fiber protein is of an adenovirus of a subgroup C origin.

Turning to claim 60, applicants propose to amend it to be directed to a recombinant adenovirus having a capsid with an increased tropism for smooth muscle cells. The recombinant adenovirus comprises a chimeric fiber protein comprising at least the knob domain of a fiber protein of an adenovirus selected from the group consisting of adenovirus 11, adenovirus 16, adenovirus 35, and adenovirus 51. A remaining part of the chimeric fiber protein is of an adenovirus of a subgroup C origin.

The as-filed specification provides working examples of the recombinant adenovirus of claim 44, the recombinant adenovirus capsid of claim 58, and the recombinant adenovirus of claim 60. For instance, the as-filed specification discloses the recombinant adenoviruses having chimeric fiber proteins designated as Ad5Fib11, Ad5Fib35, Ad5Fib51, and AdFib16 in the specification. (*See*, Specification as-filed at page 41, line 34 and page 42, lines 22 through 30). The recombinant adenoviruses originate from adenovirus 5, or a subgroup C origin, and have a chimeric fiber protein having at least a knob portion from adenovirus 11, adenovirus 16, adenovirus 35, and adenovirus 51. (*See*, *Id.* at FIG. 5, FIG. 6 and page 42 under heading "C) Subgroup B fiber mutants other than fiber 16 for generation of the recombinant adenoviruses.") The recombinant adenoviruses were used to infect HUVsmcs and as illustrated in FIG. 8d, the recombinant adenoviruses having knob proteins from adenovirus 11, adenovirus 16, adenovirus 35 and adenovirus 51 were able to infect smooth muscle cells better than an adenovirus of a subgroup C origin. (*See*, *Id.* at FIG. 8d and page 42, lines 9-30).

Thus, one of ordinary skill in the art would be able to make and use the recombinant adenovirus and capsid having an increased tropism for smooth muscle cells as recited in claims 44, 58, and 60 without undue experimentation.

Reconsideration and withdrawal of the enablement rejections of claims 2, 21, 25, 37, 44, 51, 54, 56-62, 65, 69, and 71 are requested.

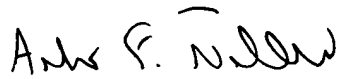
ENTRY OF AMENDMENTS

The proposed amendments to claims 2, 25, 37, 44, 58, 60, 65, 69 and 71 should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings and do not add any new matter to the application. The proposed amendments should also be entered since they comply with requirements as to form, *i.e.*, they remove 35 U.S.C. § 112, first paragraph, rejections. Further, the amendments do not raise new issues or require a further search since the amendments incorporate elements from dependent claims into independent claims. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the foregoing amendments and remarks, the applicants respectfully submit that the claims define patentable subject matter. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Office is invited to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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